FORM PTO-1390 (REV. 11-2000) U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
Mo-6341/LeA 33,270	
U S APPLICATION NO (If known, see 37 CFR 1.5	09/856571
To Be Assigned	

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/08778	November 15, 1999	November 15, 1998

TITLE OF INVENTION SEMI-HYDROCHLORIDE OF 8-CYAN-1-CYCLOPROPYL-7-(1S,6S-2,8-DIAZABICYCLO [4.3.0]NONAN-8-YL)-6-FLUORO-1,4-DIHYDRO-4-OXO-3-QUINOLINE CARBOXYLIC ACID

APPLICANT(S) FOR DO/EO/US HIMMLER, Thomas and RAST, Hubert

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND or SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. [X] The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is attached hereto (required only if not communicated by the International Bureau).
   b. [ ] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [ ] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).
7. [ ] Amendments to the claims of the International Aplication under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English lanugage translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [X] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
14. [ ] A SECOND or SUBSEQUENT preliminary amendment.
15. [ ] A substitute specification.
16. [ ] A change of power of attorney and/or address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. [X] Other items or information:

Drawings (6 sheets)
Form PTO 1449

U.S. APPLICATION NO (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
To Be Assigned 09/856571	PCT/EP99/08778	Mo-6341/LeA 33,270

21. [X] The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):

		CALCULATIONS PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a (2)) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1000.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO	$860.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$710.00	
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$690.00	
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =		$ 860.00
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).		$ 0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	11 -20 =	0	x $18.00	$ 0.00
Independent claims	3 -3 =	0	x $80.00	$ 0.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $270.00	$ 270.00
TOTAL OF ABOVE CALCULATIONS =				$ 1,130.00
[ ] Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.			+	$ 0.00
SUBTOTAL =				$ 1,130.00
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$ 0.00
TOTAL NATIONAL FEE =				$ 1,130.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 40.00
TOTAL FEES ENCLOSED =				$ 1,170.00
				Amount to be refunded: $
				charged: $

a. [ ] A check in the amount of $ _____ to cover the above fees is enclosed.

b. [X] Please charge my Deposit Account No. 13-3848 in the amount of $ 1,170.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-3848. A duplicate copy of this sheet is enclosed.

d. [ ] Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137 (a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO.

00157
PATENT TRADEMARK OFFICE

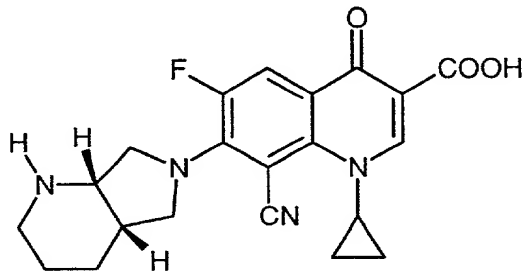
SIGNATURE

Godfried R. Akorli
NAME

28,779
REGISTRATION NUMBER

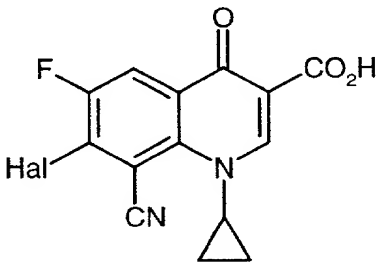
Semi-hydrochloride of 8-cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo[4.3.0]-nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

The present invention relates to a semi-hydrochloride of 8-cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, to processes for its preparation and to antibacterial compositions comprising it. 8-Cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid of the formula (I) is to be referred to as CCDC hereinbelow.



(I)

CCDC is known from DE-A 19 633 805 or PCT Appl.-No. 97 903 260.4. It is prepared by reacting 7-halogeno-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolincarboxylic acid of the formula (II)



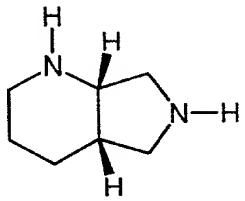
(II),

in which

Hal represents fluorine or, preferably, represents chlorine

with

(1S,6S)-2,8-diazabicyclo[4.3.0]nonane of the formula (III)

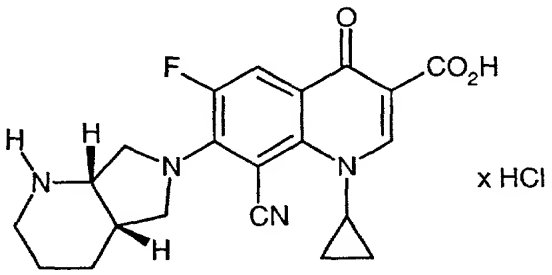


(III)

in the presence of an auxiliary base in a suitable solvent.

CCDC of the formula (I) can be used to prepare solutions in water of about 0.02% strength (w/w). For pracitical applications (solutions for injections or oral administration forms), this solubility is insufficient. Many other quinolonecarboxylic acids are known to be used for formulations in the form of certain salts. Salts which are suitable for this purpose are, on the one hand, metal salts of quinolonecarboxylic acid (for example alkali metal carboxylates) and, on the other hand, acid addition products (protonation of basic centres in the amine radical of the substituted quinolonecarboxylic acids). Acid addition products which are frequently used are, for example, mesylates, tosylates and hydrochlorides. Hydrochlorides can be prepared in a particularly simple manner, they are pharmaceutically acceptable and they have considerably better solubilities than the neutral compounds.

The CCDC hydrochloride of the formula (IV)



(IV)

is known from WO 97/31001.

It can be characterized by its X-ray powder diffractogram, by differential thermoanalysis (DTA) and by its infrared spectrum (IR).

The X-ray powder diffractogram has the reflection signals (2 theta) of high and medium intensity (> 30% relative intensity) shown in Table 1.

Table 1: X-Ray powder diffractogram of CCDC hydrochloride of the formula (IV)

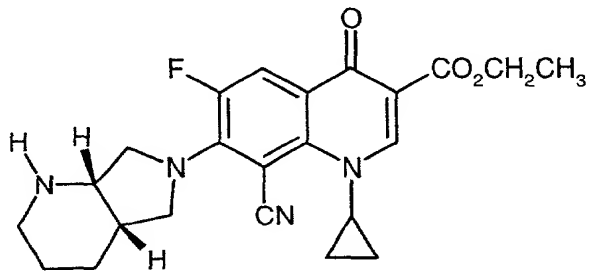
2 θ (2 theta)
6.70
13.11
15.63
25.69
25.90

The X-ray powder diffractogram of CCDC hydrochloride of the formula (IV) is also shown in Figure 1.

The melting point, determined by DTA, of CCDC hydrochloride of the formula (IV) is from 305°C to 307°C (with decomposition). The differential thermodiagram is shown in Figure 2.

The IR spectrum of CCDC hydrochloride of the formula (IV) is shown in Fig. 3.

CCDC hydrochloride of the formula (IV) can be prepared by methods which are known in principle. Thus, it is possible, for example, to admix a solution of CCDC of the formula (I) in water with a molar equivalent of HCl and to evaporate the solution to dryness. Another method consists in hydrolyzing ethyl 8-cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline-carboxylate of the formula (V)

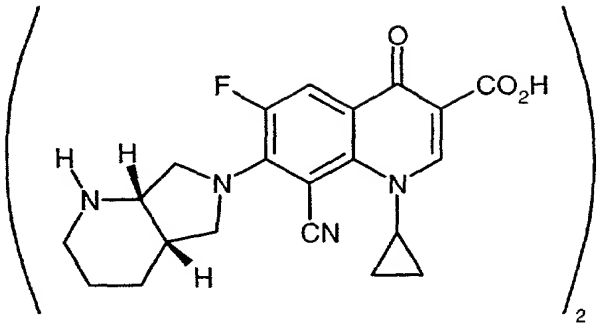


(V)

in aqueous hydrochloric acid and to isolate the precipitated CCDC hydrochloride of the formula (IV).

CCDC hydrochloride of the formula (IV) can be used to prepare a solution in water of a strength of approximately 2.8% (w/w). Thus it is more readily water-soluble than CCDC of the formula (I), but not to an extent which is desirable for all formulations.

According to the invention, it has been found that, surprisingly, the CCDC semihydrochloride of the formula (VI)



x HCl (VI)

has a particularly high solubility in water. CCDC semihydrochloride of the formula (VI) can be used to prepare solutions in water having a strength of 19% (w/w).

The invention accordingly provides crystalline CCDC semihydrochloride of the formula (VI) which is, inter alia, characterized in that it has an X-ray powder diffractogram with the reflection signals of high and medium intensity (> 30% relative intensity) given in Table 2.

Table 2: X-Ray powder diffractogram of CCDC semihydrochloride of the formula (VI)

2 θ (2 theta)
5.86
6.90
7.26
8.98
9.35
10.13
10.68
10.97
12.41
13.67
14.57
14.89
15.73
16.07
16.47
16.87
17.78
18.91
19.81
20.04
20.62
20.75
20.93
21.46
21.74
22.92
25.36
25.71
26.98
27.58
28.24
30.61

The X-ray powder diffractogram of CCDC semihydrochloride of the formula (VI) is shown in Figure 4.

The CCDC semihydrochloride of the formula (VI) is furthermore characterized in that it has a melting point, determined by differential thermoanalysis, of from 278°C to 280°C. The corresponding differential thermodiagram is shown in Figure 5.

The CCDC semihydrochloride of the formula (VI) according to the invention is furthermore characterized in that it has an infrared spectrum, measured in KBr, as shown in Figure 6.

CCDC semihydrochloride of the formula (VI) of an undetermined crystal form can be prepared by processes known in principle, for example by admixing a solution of CCDC of formula (I) in water with half a molar equivalent of HCl and evaporating the solution to dryness.

Likewise, it is possible in principle to admix such amounts of CCDC of the formula (I) and CCDC hydrochloride of the formula (IV) in a molar ratio of one to one in water such that the total concentration remains less than 20%. The resulting solution can subsequently be evaporated to dryness.

Moreover, it has been found according to the invention that, surprisingly, a CCDC semihydrochloride of the formula (VI) which is characterized by the X-ray powder diffractogram shown above and the differential thermodiagram shown above can be prepared directly.

The present invention therefore furthermore provides the CCDC semihydrochloride of the formula (VI) which is characterized in that 7-halogeno-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolonecarboxylic acid of the formula (II), in which halogen represents fluorine or, preferably, represents chlorine, is reacted with (1S,6S)-2,8-diazabicyclo[4.3.0]nonane of the formula (III), if appropriate in the presence of a base, in one of the following diluents or diluent mixtures:

a) aliphatic alcohols having at least four carbon atoms, such as, for example, butanol, isobutanol, 2-butanol, tert-butanol, 1-pentanol,

b) mixture of aliphatic alcohols having at least three carbon atoms such as, for example, propanol, isopropanol, butanol, isobutanol, 2-butanol, tert-butanol or 1-pentanol, with the polar aprotic solvent N-methylpyrrolidone,

c) mixture of propanol and N,N-dimethylformamide,

or

d) mixture of ethanol with N-methyl-pyrrolidone with added tertiary amine base, such as, for example, tripropylamine, tributylamine, N-ethylmorpholine, N-propylmorpholine and/or N-butylmorpholine.

In the preferred preparation variants with a diluent mixture according to b) or c), the mixing ratio is from 1:1 to 3:1 and, in particularly preferred embodiments, from 1:1 to 2:1.

Suitable bases according to the preparation variants with the diluents and the diluent mixtures according to a) to c) are tertiary amines, such as, triethylamine, tripropylamine, ethyl-diisopropylamine (Hünig base), tributylamine, N-ethylmorpholine, N-propylmorpholine and N-butylmorpholine.

In the preparation variants a) to d), preference is given to those embodiments where an excess of (1S,6S)-2,8-diazabicyclo[4.3.0]nonane of the formula (III) is employed.

In the preparation variants according to a) to d), preferably from 1 to 2 mol of base, particularly preferably from 1.1 to 1.5 mol of base, are employed per mole of the compound (II).

The reaction in the preparation variants according to a) to d) is carried out at atmospheric pressure or at elevated pressure between 1 bar and 100 bar, preferably between 1 bar and 20 bar.

The reaction in the preparation variants according to a) to d) is carried out at temperatures between 0°C and 200°C, preferably between 20°C and 150°C.

Preferably from 1 to 2 mol, particularly preferably from 1 to 1.5 mol, of the compound (III) are employed per mole of the compound (II).

CCDC semihydrochloride of the formula (VI) precipitates out of the reaction mixture and can be filtered off with suction. The solid which has been filtered off with suction can, if appropriate, be purified by washing with the alcohol used in the reaction.

The starting materials of the formulae (II) and (III) for preparing CCDC are known (cf. DE-A 19 633 805).

CCDC semihydrochloride of the formula (VI) is highly active against pathogenic bacteria in the area of human or veterinary medicines. Its broad area of use corresponds to that of CCDC.

The X-ray powder diffractogram for characterizing the crystal modifications of CCDC hydrochloride and CCDC semihydrochloride were obtained using a transmission diffractometer STADI-P with location-sensitive detector (PSD2) from Stoe.

The melting point of the differential thermoanalysis was obtained using the DSC 820 unit from Mettler-Toledo. The sample was heated in the air in an aluminium crucible using 20 K/min.

The IR spectrum was recorded in KBr using the FTS 60 A unit from Biorad.

The examples below illustrate the invention without limiting it. The diluents/base systems described in the examples below are particularly preferred.

5

Comparative Example

Preparation of CCDC hydrochloride of the formula (IV)

850 g of ethyl 8-cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylate are initially charged in a mixture of 1600 ml of water and 800 ml of 10% strength hydrochloric acid. The reaction mixture is heated to the boil, with the ester going into solution and the product soon beginning to precipitate out. The suspension is heated at the boil for 3 hours. It is then allowed to cool to approximately 50°C, and 1500 ml of ethanol are added. The reaction mixture is cooled to 0°C and stirred at this temperature for 1 hour. The solid is filtered off with suction, washed with 1000 ml of ethanol and dried at 60°C until the weight remains constant. This gives 845.5 g of a beige solid.

Elemental analysis (calculated values for the hydrochloride $C_{21}H_{22}ClFN_4O_3$, molecular weight 432.89):

Carbon: found 58.2% (calc. 58.27%)

Hydrogen: found 5.1% (calc. 5.12%)

Chlorine: found 8.1% (calc. 8.19%).

The product has the X-ray powder diffractogram shown in Figure 1, the differential thermodiagram shown in Figure 2 and the IR spectrum shown in Figure 3.

Preparation of CCDC semihydrochloride of the formula (VI)

Example 1

9.2 g of 7-chloro-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid are initially charged in a mixture of 30 ml of butanol, 18 ml of N-methyl-pyrrolidone and 4.85 g of Hünig base. The mixture is heated to reflux, and 4.17 g of (1S,6S)-2,8-diazabicyclo[4.3.0]nonane are then added dropwise. After the

dropwise addition has ended, stirring under reflux is continued for 3 hours and the mixture is then allowed to cool to room temperature, and the solid is filtered off with suction, washed with a total of 20 ml of butanol and dried in a vacuum drying oven at from 60 to 70°C until the weight remains constant.

This gives 8.54 g of a beige solid which has the X-ray powder diffractogram shown in Figure 4 and the differential thermodiagram shown in Figure 5.

Elemental analysis (calculated values for the CCDC semihydrochloride $C_{21}H_{22.5}Cl_{0.5}FN_4O_3$, molecular weight 414.658):
Chlorine: found 4.2% (calc. 4.275%).

Example 2

A mixture of 9.2 g of 7-chloro-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 60 ml of butanol and 4.85 g of Hünig base is heated to reflux. 4.17 g of (1S,6S)-2,8-diazabicyclo[4.3.0]nonane are added dropwise, and the mixture is then stirred under reflux for 3 hours. The solid is filtered off with suction at room temperature, washed with a total of 20 ml of butanol and dried until the weight remains constant. This gives 10.6 g of a beige solid whose differential thermodiagram corresponds to that of CCDC semihydrochloride of the formula (VI).

Elemental analysis (calculated values for the CCDC semihydrochloride $C_{21}H_{22.5}Cl_{0.5}FN_4O_3$, molecular weight 414.658):

Carbon:	found 60.55% (calc. 60.83%)
Hydrogen:	found 5.3% (calc. 5.23%)
Chlorine:	found 4.2% (calc. 4.275%)
Nitrogen:	found 13.5% (calc. 13.51%)
Oxygen:	found 11.7% (calc. 11.58%).

Example 3

A mixture of 4.6 g of 7-chloro-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 15 ml of propanol, 9 ml of N-methyl-pyrrolidone and 2.42 g of Hünig base is heated to reflux. 2.08 g of (1S,6S)-2,8-diazabicyclo-[4.3.0]nonane are added dropwise, and the mixture is then stirred under reflux for 3 hours. The solid is filtered off with suction at room temperature, washed with a total of 10 ml of propanol and dried until the weight remains constant. This gives 4.6 g of a beige solid whose differential thermodiagram corresponds to that of CCDC semihydrochloride.

Elemental analysis (calculated values for the CCDC semihydrochloride $C_{21}H_{22.5}Cl_{0.5}FN_4O_3$, molecular weight 414.658):

Chlorine: found 4.3% (calc. 4.275%).

Example 4

A mixture of 4.6 g of 7-chloro-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 15 ml of isopropanol, 9 ml of N-methyl-pyrrolidone and 2.42 g of Hünig base is heated to reflux. 2.08 g of (1S,6S)-2,8-diazabicyclo-[4.3.0]nonane are added dropwise, and the mixture is then stirred under reflux for 3 hours. The solid is filtered off with suction at room temperature, washed with a total of 10 ml of isopropanol and dried until the weight remains constant. This gives 5.3 g of a beige solid.

Elemental analysis (calculated values for the CCDC semihydrochloride $C_{21}H_{22.5}Cl_{0.5}FN_4O_3$, molecular weight 414.658):

Chlorine: found 4.2% (calc. 4.275%).

Example 5

A mixture of 4.6 g of 7-chloro-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 15 ml of 2-butanol, 9 ml of N-methyl-pyrrolidone and 2.42 g of Hünig base is heated to reflux. 2.08 g of (1S,6S)-2,8-diazabicyclo-[4.3.0]nonane are added dropwise, and the mixture is then stirred under reflux for 3 hours. The solid is filtered off with suction at room temperature, washed with a total of 10 ml of 2-butanol and dried until the weight remains constant. This gives 5.48 g of a beige solid whose differential thermodiagram corresponds to that of CCDC semihydrochloride of the formula (VI).

Elemental analysis (calculated values for the CCDC semihydrochloride $C_{21}H_{22.5}Cl_{0.5}FN_4O_3$, molecular weight 414.658):

Chlorine: found 4.2% (calc. 4.275%).

Example 6

A mixture of 4.6 g of 7-chloro-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 15 ml of isobutanol, 9 ml of N-methyl-pyrrolidone and 2.42 g of Hünig base is heated to reflux. 2.08 g of (1S,6S)-2,8-diazabicyclo-[4.3.0]nonane are added dropwise, and the mixture is then stirred under reflux for 3 hours. The solid is filtered off with suction at room temperature, washed with a total of 10 ml of isobutanol and dried until the weight remains constant. This gives 4.99 g of a beige solid whose differential thermodiagram corresponds to that of CCDC semihydrochloride of the formula (VI).

Elemental analysis (calculated values for the CCDC semihydrochloride $C_{21}H_{22.5}Cl_{0.5}FN_4O_3$, molecular weight 414.658):

Chlorine: found 4.2% (calc. 4.275%).

Example 7

A mixture of 4.6 g of 7-chloro-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 15 ml of tert-butanol, 9 ml of N-methyl-pyrrolidone and 2.42 g of Hünig base is heated to reflux. 2.08 g of (1S,6S)-2,8-diazabicyclo-[4.3.0]nonane are added dropwise, and the mixture is then stirred under reflux for 3 hours. The solid is filtered off with suction at room temperature, washed with a total of 10 ml of hot tert-butanol and dried until the weight remains constant. This gives 5.38 g of a beige solid whose differential thermodiagram corresponds to that of CCDC semihydrochloride of the formula (VI).

Elemental analysis (calculated values for the CCDC semihydrochloride $C_{21}H_{22.5}Cl_{0.5}FN_4O_3$, molecular weight 414.658):

Chlorine: found 4.2% (calc. 4.275%).

Example 8

A mixture of 4.6 g of 7-chloro-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 15 ml of 1-pentanol, 9 ml of N-methyl-pyrrolidone and 2.42 g of Hünig base is heated to reflux. 2.08 g (1S,6S)-2,8-diazabicyclo-[4.3.0]nonane are added dropwise, and the mixture is then stirred under reflux for 3 hours. The solid is filtered off with suction at room temperature, washed with a total of 10 ml of 1-pentanol and dried until the weight remains constant. This gives 3.0 g of a beige solid whose differential thermodiagram corresponds to that of CCDC semihydrochloride of the formula (VI).

Elemental analysis (calculated values for the CCDC semihydrochloride $C_{21}H_{22.5}Cl_{0.5}FN_4O_3$, molecular weight 414.658):

Chlorine: found 4.3% (calc. 4.275%).

Example 9

A mixture of 4.6 g of 7-chloro-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 15 ml of ethanol, 9 ml of N-methyl-pyrrolidone and 3.47 g of tributylamine is heated to reflux. 2.08 g of (1S,6S)-2,8-diazabicyclo[4.3.0]nonane are added dropwise, and the mixture is then stirred under reflux for 3 hours. The solid is filtered off with suction at room temperature, washed with a total of 10 ml of ethanol and dried until the weight remains constant. This gives 5.0 g of a beige solid whose differential thermodiagram corresponds to that of CCDC semihydrochloride of the formula (VI).

Elemental analysis (calculated values for the CCDC semihydrochloride $C_{21}H_{22.5}Cl_{0.5}FN_4O_3$, molecular weight 414.658):

Chlorine: found 4.2% (calc. 4.275%).

Example 10

A mixture of 4.6 g of 7-chloro-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 15 ml of ethanol, 9 ml of N-methyl-pyrrolidone and 2.16 g of N-ethylmorpholine is heated to reflux. 2.08 g of (1S,6S)-2,8-diazabicyclo-[4.3.0]nonane are added dropwise, and the mixture is then stirred under reflux for 3 hours. The solid is filtered off with suction at room temperature, washed with a total of 10 ml of ethanol and dried until the weight remains constant. This gives 5.4 g of a beige solid.

Elemental analysis (calculated values for the CCDC semihydrochloride $C_{21}H_{22.5}Cl_{0.5}FN_4O_3$, molecular weight 414.658):

Chlorine: found 4.3% (calc. 4.275%).

Example 11

A mixture of 4.6 g of 7-chloro-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, 15 ml of propanol, 9 ml of N,N-dimethylformamide and 2.42 g of Hünig base is heated to reflux. 2.08 g of (1S,6S)-2,8-diazabicyclo-[4.3.0]nonane are added dropwise, and the mixture is then stirred under reflux for 3 hours. The solid is filtered off with suction at room temperature, washed with a total of 10 ml of propanol and dried until the weight remains constant. This gives 4.4 g of a beige solid.

Elemental analysis (calculated values for the CCDC semihydrochloride $C_{21}H_{22.5}Cl_{0.5}FN_4O_3$, molecular weight 414.658):

Chlorine: found 4.2% (calc. 4.275%).

Patent Claims

1. Semi-hydrochloride of 8-cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo-[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid.

2. Semi-hydrochloride of 8-cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo-[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (CCDC semihydrochloride), characterized in that it has an X-ray powder diffractogram with the following reflection signals (2 theta) of high and medium intensity.

2 θ (2 Theta)
5.86
6.90
7.26
8.98
9.35
10.13
10.68
10.97
12.41
13.67
14.57
14.89
15.73
16.07
16.47
16.87
17.78
18.91
19.81
20.04
20.62
20.75
20.93
21.46
21.74
22.92
25.36
25.71
26.98
27.58

28.24
30.61

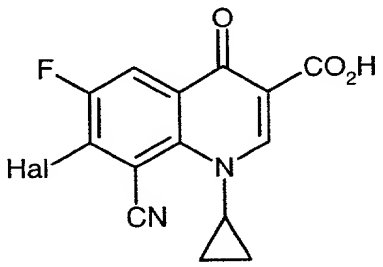
3. Semi-hydrochloride of 8-cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo-[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (CCDC semihydrochloride), characterized in that it has an X-ray powder diffractogram with the following reflection signals (2 theta) of high and medium intensity.

2 θ (2 Theta)
5.86
6.90
7.26
8.98
9.35
10.13
10.68
10.97
12.41
13.67
14.57
14.89
15.73
16.07
16.47
16.87
17.78
18.91
19.81
20.04

20.62
20.75
20.93
21.46
21.74
22.92
25.36
25.71
26.98
27.58
28.24
30.61

and a melting point, determined by DTA, of from 278°C to 280°C.

4. CCDC semihydrochloride according to Claim 1 or 2, obtainable by reacting 7-halogeno-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinoline-carboxylic acid of the formula (II)

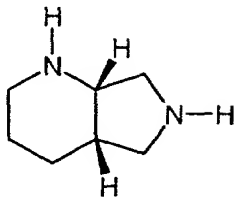


(II),

in which

Hal represents fluorine or chlorine,

and (1S,6S)-2,8-diazabicyclo[4.3.0]nonane of the formula (III)



(III),

if appropriate in the presence of a base, in one of the following diluents or diluent mixtures:

a) aliphatic alcohols having at least four carbon atoms,

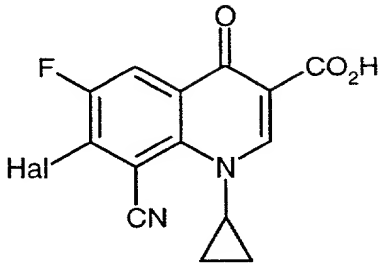
b) mixture of, for example, aliphatic alcohols having at least three carbon atoms with the diluent N-methylpyrrolidone,

c) mixture of propanol and N,N-dimethylformamide,

or

d) mixture of ethanol with N-methyl-pyrrolidone with added tripropylamine, tributylamine, N-ethylmorpholine, N-propyl-morpholine and/or N-butylmorpholine base.

5. Process for preparing CCDC semihydrochloride according to any of Claims 1 to 4, characterized in that 7-halogeno-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid of the formula (II)

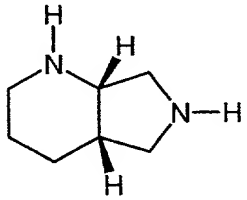


(II),

in which

Hal represents fluorine or represents chlorine

and (1S,6S)-2,8-diazabicyclo[4.3.0]nonane of the formula (III)



(III)

are reacted in the presence of a base in one of the following diluents or diluent mixtures:

a) aliphatic alcohols having at least four carbon atoms,

b) mixture of, for example, aliphatic alcohols having at least three carbon atoms with the diluent N-methylpyrrolidone,

c) mixture of propanol and N,N-dimethylformamide,

or

d) mixture of ethanol with N-methyl-pyrrolidone with added tripropylamine, tributylamine, N-ethylmorpholine, N-propyl-morpholine and/or N-butylmorpholine base.

6. Process for preparing CCDC semihydrochloride according to Claim 5, characterized in that the diluent used is an aliphatic alcohol having at least 4 carbon atoms or that an aliphatic alcohol having at least two carbon atoms is used as component of a diluent mixture.

7. Process for preparing CCDC semihydrochloride according to Claim 5, characterized in that, if an aliphatic alcohol having at least 3 carbon atoms is used as component of a diluent mixture, N-methyl-pyrrolidone is simultaneously employed as a further diluent in a ratio of from 1 to 1 to 3 to 1.

8. Process for preparing CCDC semihydrochloride according to Claim 6, characterized in that, if propanol is used as component of a diluent mixture, N,N-dimethylformamide is simultaneously employed as further diluent in a ratio of from 1 to 1 to 3 to 1.

9. Medicament, characterized in that it comprises, in addition to customary auxiliaries and excipients, CCDC semihydrochloride according to any of Claims 1 to 4.

10. Use of CCDC semihydrochloride according to any of Claims 1 to 4 for preparing medicaments.

11. Use of CCDC semihydrochloride according to any of Claims 1 to 4 in antibacterial compositions.

Semi-hydrochloride of 8-cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo[4.3.0]-nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid

Abstract

The present invention relates to a semi-hydrochloride of 8-cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, to processes for its preparation and to antibacterial compositions comprising it. The semihydrochloride of 8-cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid can be described by the following formula:

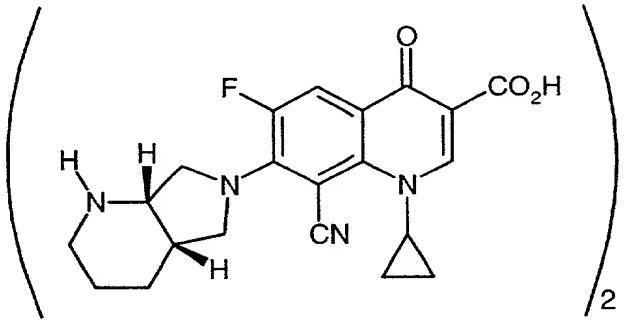


Fig.1

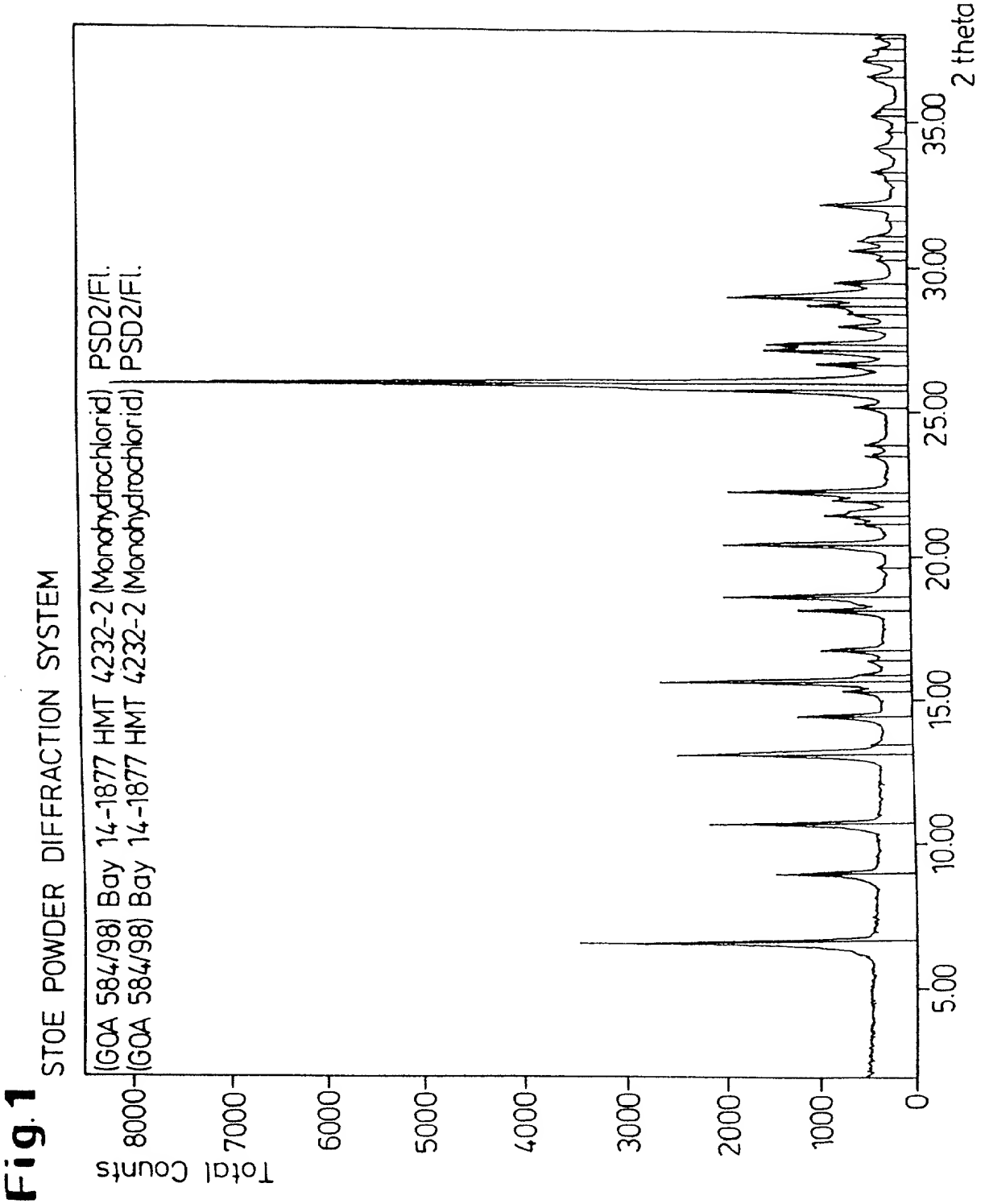

STOE POWDER DIFFRACTION SYSTEM
(GOA 584/98) Bay 14-1877 HMT 4232-2 (Monohydrochlorid) PSD2/Fl.
(GOA 584/98) Bay 14-1877 HMT 4232-2 (Monohydrochlorid) PSD2/Fl.
Total Counts
8000
7000
6000
5000
4000
3000
2000
1000
0
5.00
10.00
15.00
20.00
25.00
30.00
35.00
2 theta

Fig. 2

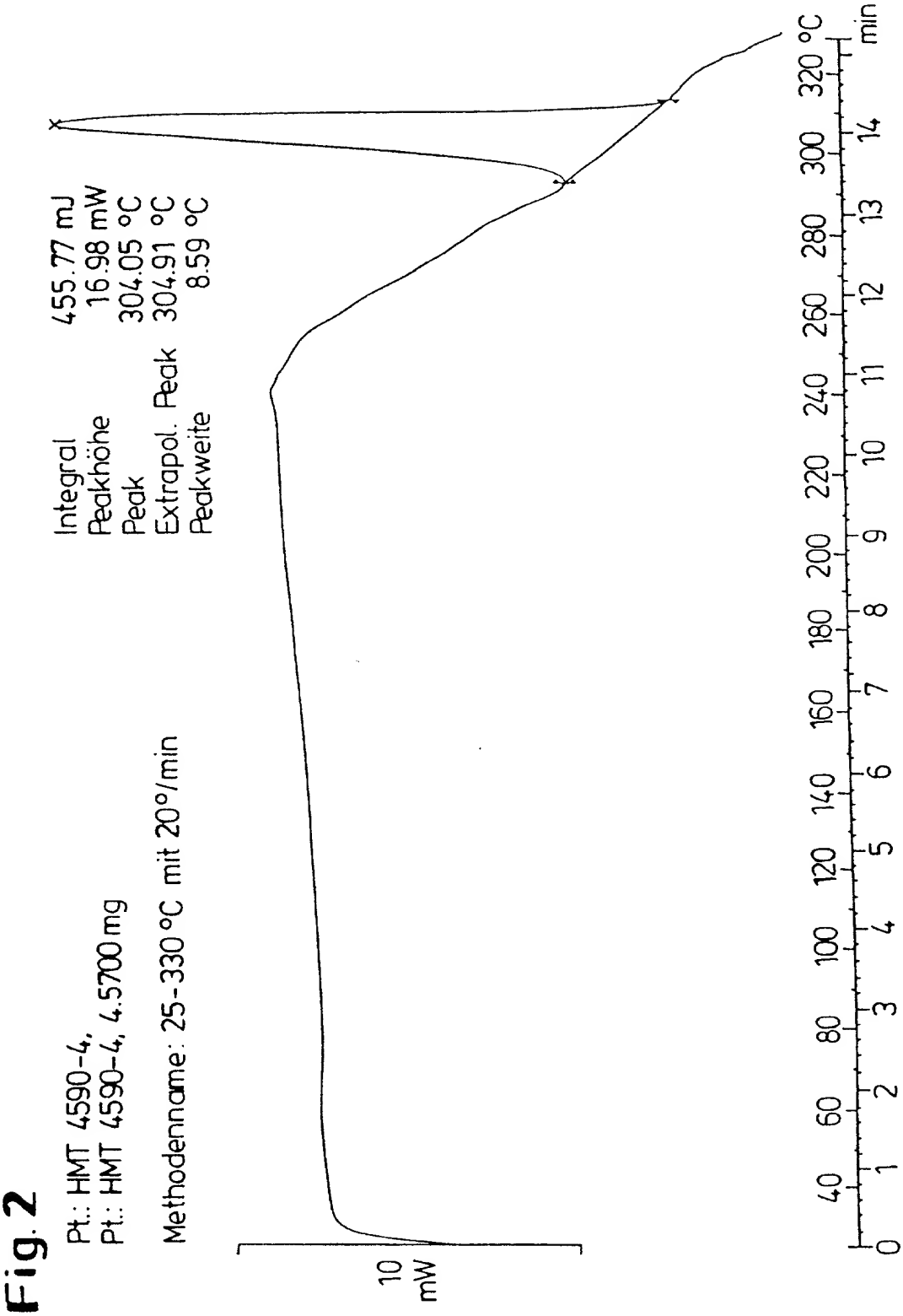

Pt.: HMT 4590-4,
Pt.: HMT 4590-4, 4.5700 mg
Methodenname: 25-330 °C mit 20°/min
Integral 455.77 mJ
Peakhöhe 16.98 mW
Peak 304.05 °C
Extrapol. Peak 304.91 °C
Peakweite 8.59 °C
10 mW
40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 °C
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 min

Fig. 3

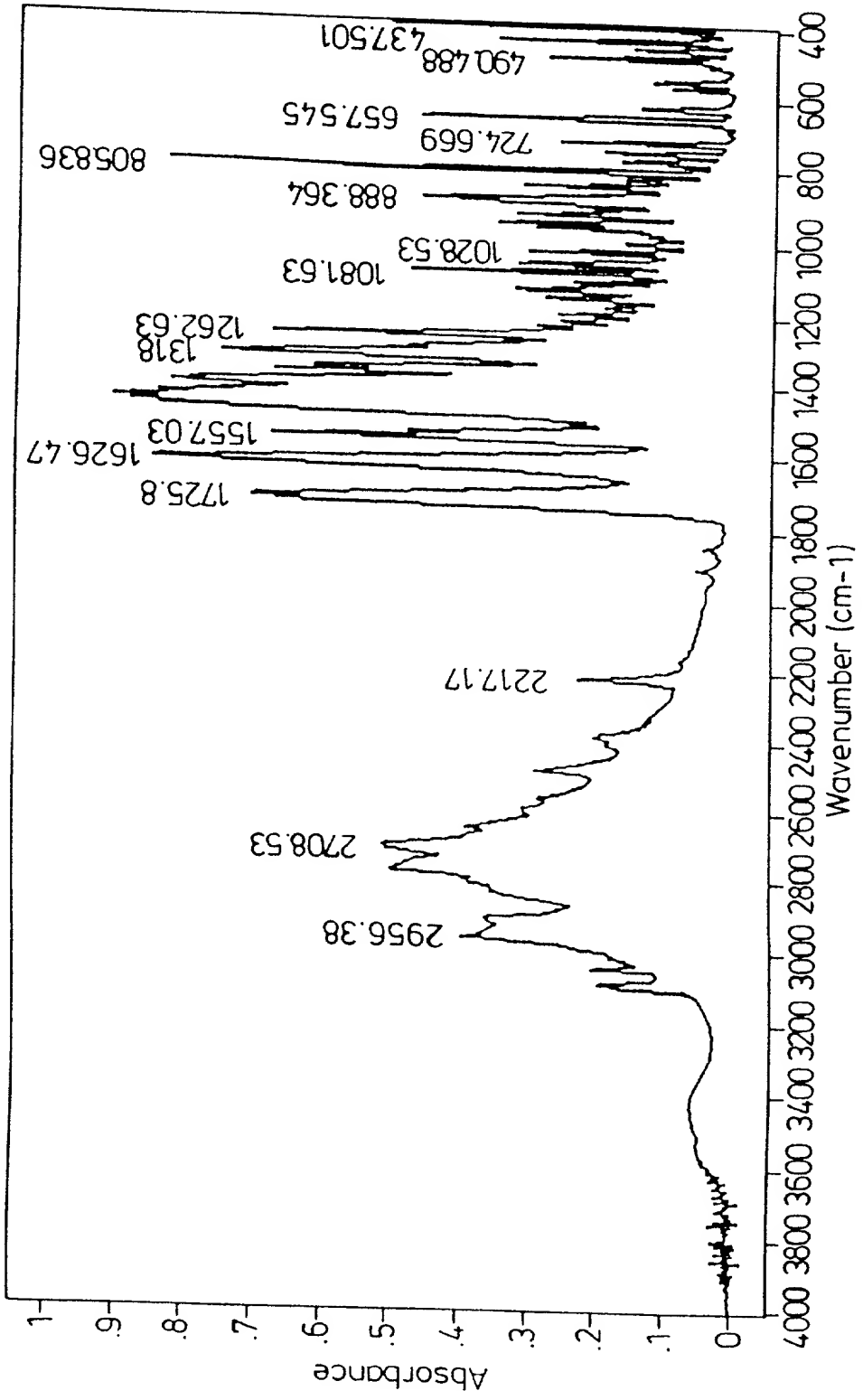


Fig. 4

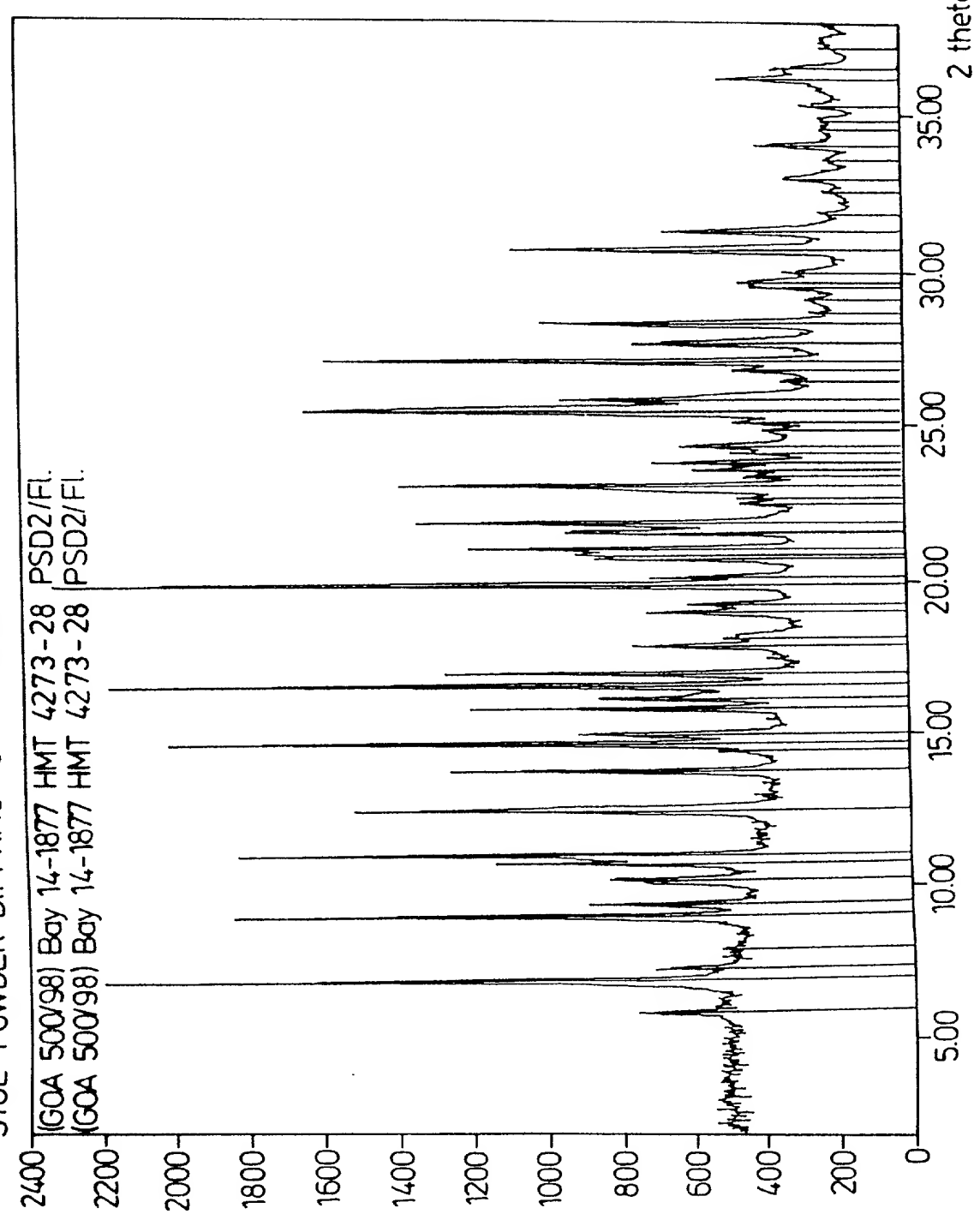

STOE POWDER DIFFRACTION SYSTEM
(GOA 500/98) Bay 14-1877 HMT 4273-28 PSD2/Fl.
(GOA 500/98) Bay 14-1877 HMT 4273-28 PSD2/Fl.
Total Counts
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
5.00
10.00
15.00
20.00
25.00
30.00
35.00
2 theta

Fig.5

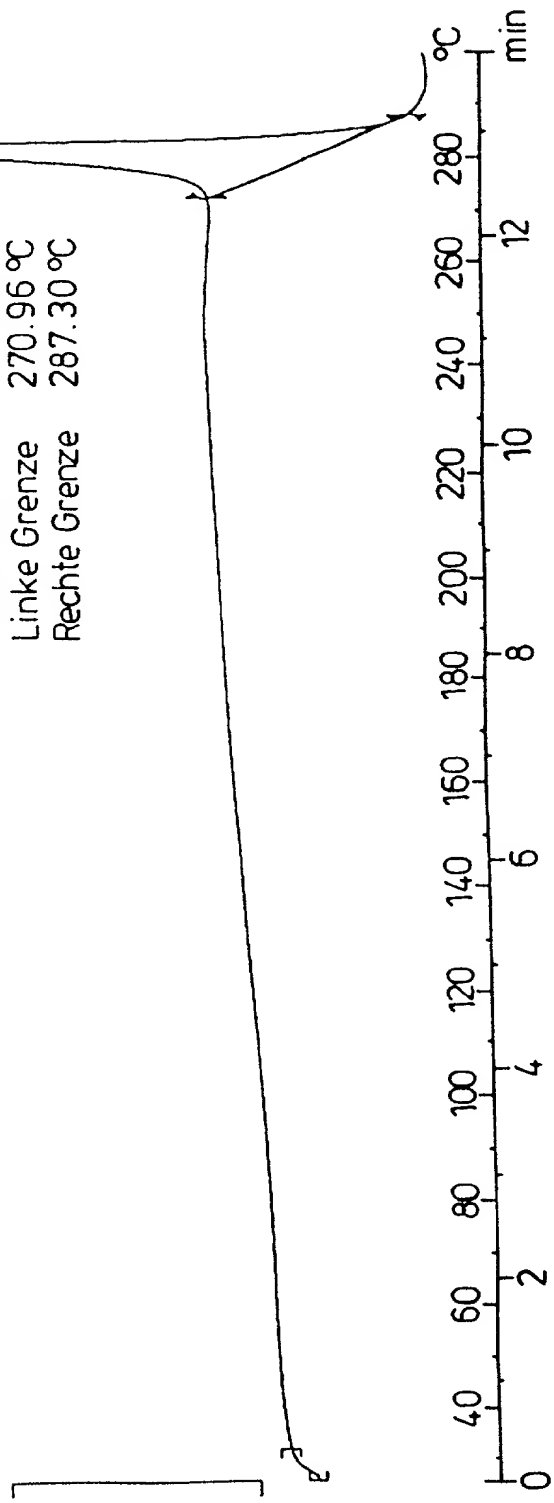
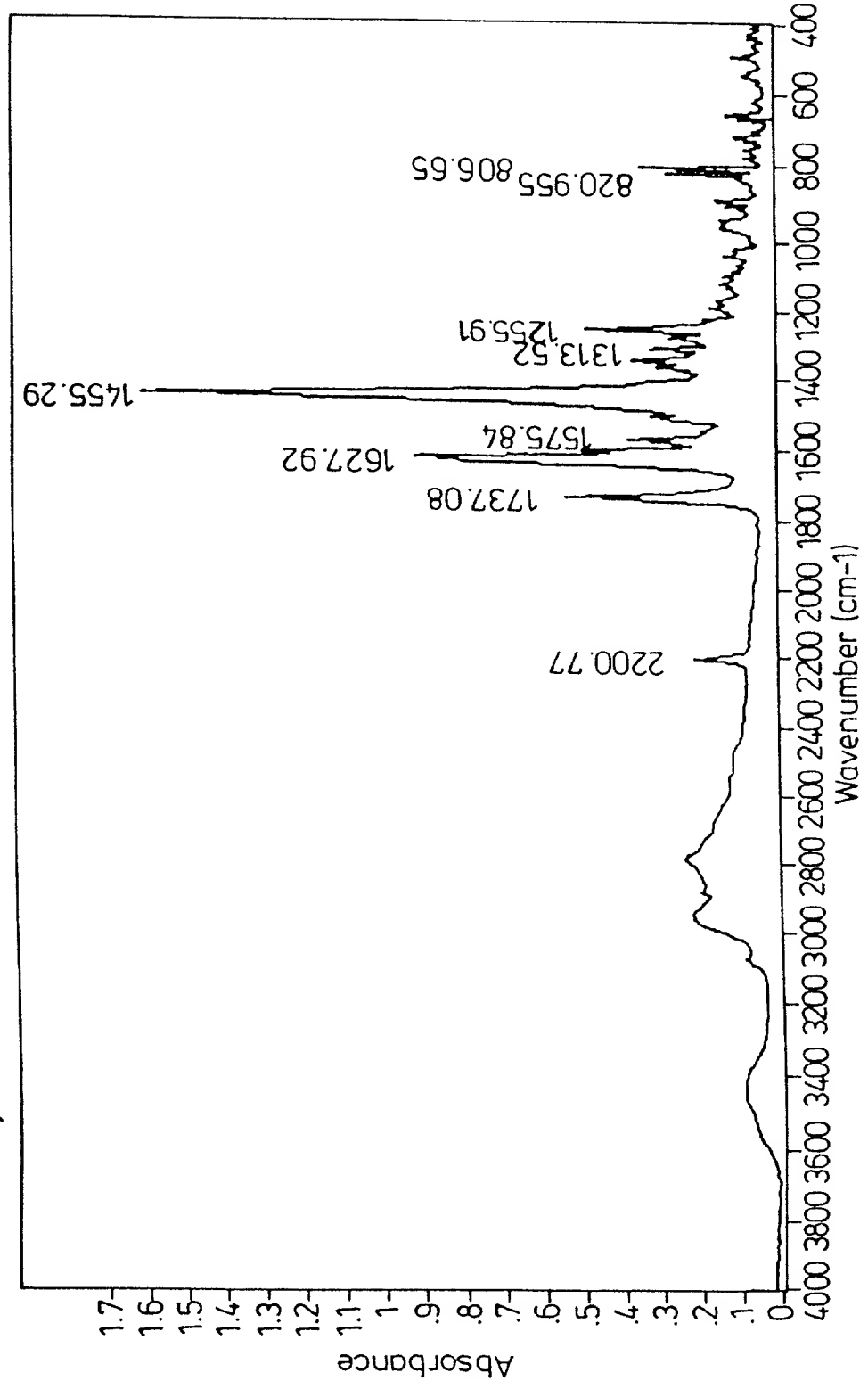

HMT 4273-51,
HMT 4273-51, 3.4500 mg
Methode: 25-300 °C mit 20°/min
25.0-300.0 °C 20.0 °C/min
Integral 295.20 mJ
Peakhöhe 20.50 mW
Peak 279.51 °C
Extrapol. Peak 279.49 °C
Peakweite 4.18 °C
Linke Grenze 270.96 °C
Rechte Grenze 287.30 °C
10 mW
40 60 80 100 120 140 160 180 200 220 240 260 280 °C
0 2 4 6 8 10 12 min

Fig.6


CCDC-Semihydrochlorid
Absorbance
Wavenumber (cm-1)
4000 3800 3600 3400 3200 3000 2800 2600 2400 2200 2000 1800 1600 1400 1200 1000 800 600 400
0 .1 .2 .3 .4 .5 .6 .7 .8 .9 1 1.1 1.2 1.3 1.4 1.5 1.6 1.7
2200.77
1737.08
1627.92
1575.84
1455.29
1313.52
1255.91
820.955
806.65

COMBINED DECLARATION AND POWER OF ATTORNEY	ATTORNEY DOCKET NO

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought
on the invention entitled

SEMI-HYDROCHLORIDE OF 8-CYAN-1-CYCLOPROPYL-7-(1S,6S-2,8-DIAZABICYCLO [4.3.0]NONAN-8-YL)-6-FLUORO-1,4-DIHYDRO-4-OXO-3-QUINOLINE CARBOXYLIC ACID

the specification of which is attached hereto,

or was filed on **November 15, 1999**

as a PCT Application Serial No. **PCT/EP99/08776**

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s), the priority(ies) of which is/are to be claimed:

198 54 357.3	**Germany**	**November 25, 1998**
(Number)	(Country)	(Month/Day/Year Filed)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose the material information as defined in Title 37, Code of Federal Regulations, §1.56 which occured between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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  ARON PREIS, Patent Office Registration Number 29,426
  LYNDANNE M. WHALEN, Patent Office Registration Number 29,457
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RESIDENCE		CITIZENSHIP
POST OFFICE ADDRESS		
FULL NAME OF FOURTH INVENTOR	INVENTOR'S SIGNATURE	DATE
RESIDENCE		CITIZENSHIP
POST OFFICE ADDRESS		
FULL NAME OF FIFTH INVENTOR	INVENTOR'S SIGNATURE	DATE
RESIDENCE		CITIZENSHIP
POST OFFICE ADDRESS		
FULL NAME OF SIXTH INVENTOR	INVENTOR'S SIGNATURE	DATE
RESIDENCE		CITIZENSHIP
POST OFFICE ADDRESS		
FULL NAME OF SEVENTH INVENTOR	INVENTOR'S SIGNATURE	DATE
RESIDENCE		CITIZENSHIP
POST OFFICE ADDRESS		